METABOLISM AND REGULATION I

TITLE: PLASMA FLUORIDE CONCENTRATION DURING HALOGENATED ANESTHETIC ADMINISTRATION WITH NORMOXIA AND HYPOXIA

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Introduction: Biotransformation of the halogenated anesthetics ordinarily follows an oxidative route of metabolism which requires oxygen and is catalyzed by the microsomal drug metabolizing enzyme system (cytochrome P-450 system). Isoflurane and enflurane are metabolized in this way to several products, one of which is inorganic fluoride ion. Halothane is oxidatively metabolized to Cl-, Br-, and trifluoroacetic acid. Widger1 reported that, under conditions in which oxygen availability is restricted, halothane is reductively metabolized by microsomes to inorganic fluoride ion. This report examines the effect of hypoxia on fluoride ion production following enflurane and isoflurane anesthesia and compares it to fluoride ion production following halothane.

Methods: Three groups of 24 male Wistar rats were chosen at random for exposure to approximately 0.5 MAC halothane, enflurane or isoflurane. For each anesthetic four subgroups of 6 animals each were established: Group 1 received an anesthetic in 50% O2 and Group 3 received the anesthetic in 100% O2. Groups 2 and 4 were pretreated with phenobarbital (1 mg/kg) in the drinking water for 4 days prior to anesthetic exposure. Following this pretreatment, Group 2 received the anesthetic in 50% O2, and Group 4 received the anesthetic in 10% O2. On the hour gas exposures were conducted in a 24 L; all glass enclosure, using a 10 L/min flow. Breathing quality air was mixed with O2 or N2 as needed using calibrated flowmeters and monitored using an oxygen analyzer. Anesthetics were vaporized from temperature compensated specific agent vaporizers which were individually calibrated so that delivered concentrations were accurately known. Following exposure to the gas mixtures the animals were killed and plasma was obtained from shed blood. Plasma fluoride ion concentrations were determined using an Orion fluoride ion electrode, reference electrode, high impedance millivoltmeter and total ionic strength buffer. All specimens were processed in plastic containers. Fluoride electrode standardization was performed using plasma standards. For each anesthetic the mean fluoride concentrations for the four subgroups were tested for significant differences using the analysis of variance. Differences between the means were considered significant if the F statistic was significant and the least significant difference of the means was less than the observed difference for any pair of means at P<0.05.

Results: Halothane administered with 50% O2 resulted in plasma fluoride concentrations of less than 2.3 μM. When Halothane was given with 100% O2, fluoride concentration was 3.1 μM without phenobarbital pretreatment and 21 μM with phenobarbital pretreatment. Enflurane resulted in higher concentrations of plasma fluoride than isoflurane in all four treatments. However, the pattern of plasma fluoride concentration for the four treatments with these two agents were similar. Plasma fluoride was greater with 50% O2 than with 10% O2 and was greater with phenobarbital than without it.

Discussion: As measured by plasma fluoride concentration, halothane is only slightly defluorinated when oxygen is adequate but is defluorinated to a much greater extent during hypoxia in rats treated with phenobarbital. This latter circumstance is associated with liver cell injury234 and binding of halothane metabolites to intracellular components24. In contrast, Harper has presented morphologic evidence that anesthesia during hypoxia with enflurane or isoflurane does not result in liver cellular injury5. Enflurane and isoflurane both require oxygen for defluorination and is enhanced by phenobarbital pretreatment, presumably through induction of the cytochrome P-450 system. During hypoxia there is no tendency for plasma fluoride concentration to increase during anesthesia with these two agents. It must be recognized that if these two anesthetics are metabolized by a reductive mechanism to products other than fluoride ion, this study would not have detected them. This report provides support for the thesis that hypoxia does not alter the metabolism of enflurane or isoflurane in a manner analogous to that which occurs with halothane.

References:

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